DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAY 16 2000 7211 '00 MAY 18 P1:29

Richard D. Marthei
Law Offices of McKenna & Cuneo
1575 Eye Street, N.W.
Washington, D.C. 20005

Re: Docket No. 80N-0146
Comment No. CP3

Dear Mr. Marthei:

This letter responds to a citizen petition (CP3) submitted on behalf of the Oakhurst Company dated February 10, 1995 under Docket No. 80N-0146 in the Dockets Management Branch. The petitioner requests that FDA establish a monograph for over-the-counter (OTC) drug products for nailbiting and thumbsucking deterrent drugs to recognize cayenne pepper as a safe and effective ingredient for use in aversive taste therapy products to deter nailbiting and thumbsucking.

Background

In 1993 the agency published a final rule (FEDERAL REGISTER of September 2, 1993 (58 FR 46749)) establishing that any nailbiting and thumbsucking deterrent drug product for OTC human use is not generally recognized as safe and effective and is misbranded (21 CFR § 310.536). On February 23, 1994, you submitted a citizen petition (CP2) on behalf of the Oakhurst Company requesting that the agency amend the regulations to delete cayenne pepper as a nonmonograph nailbiting and thumbsucking active ingredient. In a letter from William E. Gilbertson, Pharm.D. to you dated November 1, 1994, the agency determined that cayenne pepper should remain as a nonmonograph ingredient. On February 10, 1995, you submitted a citizen petition (CP3) on behalf of the Oakhurst Company in response to the agency's denial letter of November 1, 1994 requesting that FDA amend the final rule to include cayenne pepper as a safe and effective ingredient for use in aversion taste therapy products to deter nailbiting and thumbsucking.

The Division of OTC Drug Products has reviewed the data submitted with your petition and has determined that they are inadequate to establish a monograph for nailbiting and thumbsucking deterrent drug products for consideration of cayenne pepper as an active ingredient. We have following specific comments concerning the information submitted.

The Study and Results

The petitioner submitted a number of published studies concerning aversive taste therapy products. However, only two of the studies used cayenne pepper as the active ingredient and of these involved only one subject.

80N-0146

LET

The study by Vargas et al. is a randomized, controlled trial of cayenne pepper in 61 subjects (31 men and 30 women), with an average age of 19.75 years and an average of 12 years of chronic nailbiting, to compare aversion therapies for nailbiting. Eligible subjects were randomized to one of four aversion therapies: electric shock (N=16); negative practice (N=16); bitter substance (N=16); or attention-placebo control (N=13). The study comprised five experimental sessions at 1-week intervals and a sixth, follow-up session 3 weeks later. After completing the initial session, subjects were exposed to three weekly 10-minute treatment sessions. One week after the treatment period, post-treatment nail measurements were obtained.

At baseline, no significant differences existed among the treatment groups with respect to either mean fingernail length or self-monitoring data. In comparing pre-treatment nail length measures to both post-treatment and follow up measures, significant nail growth was observed in all four treatment cohorts (t-tests for correlated measures), with the self-monitoring subset achieving a significantly greater amount of nail growth. However, no significant differences in effectiveness emerged between the treatment groups. Also, the self-monitoring by treatment interactions were not significant. In a 3-month post-follow-up survey, 48 subjects were contacted and questioned as to their nailbiting status. The proportion of subjects who claimed improvement (i.e., biting less frequently or not at all) was significantly greater in each of the treatment groups compared to the control group (chi-square, $p < .05$).

The study by Knell et al. is a case report of a 39-month old developmentally normal boy with a history of cyclical, repeated trichotillomania (compulsive hair pulling). During the study, an aversive tasting substance *(Thum)* was applied to the patients thumb, initially every two hours and gradually less often, so that by the fourth month it was applied only at bedtime. The child was seen for four sessions, which included behavioral assessment and developmental testing. As a result of the intervention, the child discontinued hair pulling and thumbsucking entirely by the third day of treatment. Except for two isolated incidents of hair pulling, the behavior did not recur during the first month. Follow-up at 2, 6, and 40 months revealed only one episode of hair pulling.

Discussion

The study by Vargas et al. did not address the safety (e.g., cutaneous tolerance) of cayenne pepper, nor did the study demonstrate that the effectiveness of this ingredient was statistically superior to control treatment. As the authors point out, nail length, while an objective measure, may not have been an appropriate surrogate for thumbsucking or may have been a biased surrogate for nailbiting when the nail is bitten but not actually gnawed away. Other confounding factors may have included compliance with cayenne pepper use during the experimental period (not formally assessed), experimenter influences (particularly with the use of different experimenters in the four treatment groups), and the behavioral effect of study participation. The data in the 3-month follow-up survey appear somewhat favorable, but may not be reliable. Of the 61 subjects who completed the study through the post-treatment session, 13 were unaccounted for in this analysis. In addition, the reliability of the survey data could not be assessed, as nail

length was not measured at this time point.

The case-report by Knell et al. is of anecdotal interest, but does not constitute an adequate demonstration of the safety or effectiveness of cayenne pepper for thumbsucking.

The remainder of the references submitted did not involve treatment with cayenne pepper. Thus, they are not relevant to the request in the citizen petition.

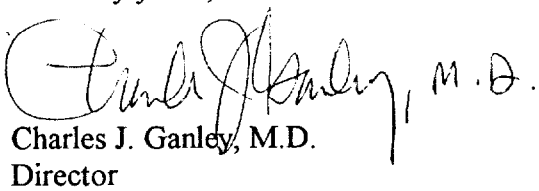
Conclusions

We find that the data submitted with your petition are not sufficient to establish safety and effectiveness for an OTC monograph for nailbiting and thumbsucking deterrent drug products. Therefore, cayenne pepper remains as a nonmonograph ingredient.

We intend to recommend to the Commissioner that the agency respond to your petition in the above manner. Any comment you wish to make on the above information, or any additional information you wish to provide, should be submitted in three copies, identified with the docket and comment numbers shown at the beginning of this letter, to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. This letter should not be considered a formal ruling on your petition. That occurs when you are sent a response by the Associate Commissioner for Regulatory Affairs.

We hope this information will be helpful.

Sincerely yours,



Charles J. Ganley, M.D.
Director
Division of OTC Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research